PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ :		(11) In	ternationa	l Publication Num	ber:	WO 92/00743
A61K 31/54	A1	(43) Int	ernstional	Poblication Date:	23	3 January 1992 (23.01.92)
(21) International Application Number: PCT/EP (22) International Filing Date: 8 July 1991		`\`		imperial House, 1		et al.; Frank B Dehn & ngsway, London WC2B
(30) Priority data: 9015108.5 9 July 1990 (09.07.90) (71) Applicant (for all designated States except US): ELLICH SÖHNE AG FÜR CHEMISCHE IND [CH/CH]; Wolhusen, CH-6110 Lucerne (CH).	O GEIS	B r-	paten tent), (Euro pean	t), CA, CH (Euro DK (European pa pean patent), GB patent), IT (Euro	pean pai itent), Es (Europ pean pat	patent), BE (European tent), DE (European pa- se (European patent), FR ean patent), GR (Euro- tent), JP, LU (European the SE (European patent),
(72) Inventor; and (75) Inventor/Applicant (for US only): MONSON, J GB]; Academic Surgical United, Queen Eliza Queen Mother Building, St Mary's Hospita Street, London W2 1NY (GB).	beth T	e	blished <i>With i</i>	international searci	h report.	
(54) Title: USE OF TAUROLIDINE AND/OR TAU	URUL	AM FO	OR THE	TREATMENT O	F TUMO	OURS

(57) Abstract

The present invention relates to a method of treatment or prophylaxis of tumours in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk to tumour growth.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

		•			
AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI .	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BP	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinca	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	· IT	Italy	RO	Romania
CF.	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic	SE	Sweden
CH		٠.	of Korea	SN	Senegal
a	Côte d'Ivoin:	KR	Republic of Korea	SU	Soviet Union
СМ	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	ш	Luxembourg	us	United States of America
DW	Dunmant	140			

USE OF TAUROLIDINE AND/OR TAURULTAM FOR THE TREATMENT OF TUMOURS
This invention relates to the treatment of tumours by
chemotherapy.

The antibacterial and anti-toxin drug taurolidine and the related product taurultam have recently been shown to exert a modifying effect on the toxicity of tumour necrosis factor (TNF) which is used, inter alia, in the treatment of tumours. Our United Kingdom Patent Application No 9005856.1 relates to combined therapy using TNF and taurolidine or taurultam. In the course of these studies, it was surprisingly found that taurolidine acted directly on tumours in addition to its effect on TNF. Furthermore, such action was shown to be selective in that the growth of normal cell-lines was not significantly inhibited.

According to the present invention we provide a method of treatment or prophylaxis of tumours in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk to tumour growth.

Taurolidine and taurultam have the formulae given below:

TAUROLIDINE

TAURULTAM

The se compounds are methylol transfer agents.

Taurolidine acts by transferring three methylol groups at the site of action, taurultam being an intermediate metabolite which itself transfers a single methylol group with liberation of the very well tolerated compound taurinamide. Thus, the two compounds act by essentially the same mechanism. It should be noted that methylol transfer is to be contrasted with methyl transfer which is characteristic of many highly toxic anti-tumour drugs. Taurolidine and taurultam have low toxicity and are not cytotoxic against normal cells.

The taurolidine or taurultam may be administered systemically, ie. by injection or infusion, or by direct application, eg topically, to external tumours.

Suitable formulations for injection or infusion may comprise an isotonic solution containing one or more solubilising agents, eg polyols such as glucose, in order to provide solutions of increased taurolidine or taurultam concentration. Such solutions are described in our European Patent Application 253662. The concentration of taurolidine or taurultam in such solutions may be in the range 1 to 10 g/litre.

Taurolidine and/or taurultam may be administered in the dose range 150 to 450 mg/kg per day, preferably 300 to 450 mg/kg per day. Relatively large volumes of aqueous solutions containing taurolidine or taurultam will thus often require to be administered, containing for example 10g to 30g of taurolidine and/or taurultam. It may be convenient to administer these compounds by infusion in view of the relatively large volumes concerned, conveniently at intervals throughout the day.

It is believed that other agents known to be involved in tumour metabolism may also advantageously be co-administered in conjunction with the above combined therapy. Such agents include gamma-interferon, interleukin-1 and interleukin-2. Cytotoxic agents such as adriamycin and actinomycin D may also be co-administered.

The tumours to be treated may be of any type, including lymphomas, sarcomas, melanomas and carcinomas. It is particularly beneficial to use taurolidine and/or taurultam prevent the spread of metastases, especially following surgical removal of tumours. The mammalian subjects are typically humans.

The invention also includes the use of taurolidine and/or taurultam for the treatment or prophylaxis of tumours in mammalian subjects.

The invention further includes the use of taurolidine and/or taurultam for the preparation of pharmaceutical compositions for the treatment or prophylaxis of tumours in mammalian subjects.

The following examples are given by way of illustration only:-

Example 1

C573L/6 mice injected iv with 1.5x10⁶ B16 melanoma cells were treated with a) ip normal saline tid on days 0-10, b) ip taurolidine 4.0mg tid on days 0-10, and c) ip taurolidine 4.0mg tid on days 3-10. Mice were sacrificed on day 10 and pulmonary metastases counted. When taurolidine treatments started on the day of tumour injection, the number of pulmonary metastases was

ĵ.

significantly reduced compared either to the control group or to Group C (p<0.05).

Treatment Group	<u>n mean Pu</u>	Imonary Metastases ± S.E.M
		•
Saline	25	117.3 ± 18.5
Taurolidine (D 0-10)	. 16	76.4 ± 14.9
Taurolidine (D 3-10)	16	103.5 ± 14.8

In a second in vivo experiment, Balb/c mice injected so with 1.5 x 10⁶ Meth A sarcoma cells received either no treatment or taurolidine 2mg ip bid for seven days. At seven days 90% (27/30) of the control animals had palpable tumour growth, while only 40% (12/30) of the taurolidine treated mice had detectable tumour growth (p-0.0.02). In a third series Balb C mice received IP injections of meth A followed by either a)saline 0.1 ml IP BD or b) taurolidine 0.1 ml IP BD for 7 days. At 7 days 28/32 saline treated mice had ascites in comparison to 0/32 of taurolidine treated mice (p<0.0001). Actuarial survival of saline treated mice was also significantly impaired (p,0.005).

Example 2

Taurolidine was tested against multiple cell lines (two tumours, one normal) using a range of doses.

Cell line	Concentration	Inhibition of
tested	(μg ml)	cellular metabolism
(%)		
Foreskin		
Fibroblasts	20	31.7
LS174T (colon)	20	84.3
Jurkat (leukaemic)	20	84.6

Preferential activity against tumour lines was demonstrated at low doses with complete cellular inhibition of tumour, but not normal cells, occurring at doses > 200 μg ml

2

CLAIMS

- 1. A method of treatment or prophylaxis of tumours in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk to tumour growth.
- 2. A method as claimed in Claim 1 wherein said taurolidine and/or taurultam is administered by injection or infusion or by direct application to external tumours.
- 3. A method as claimed in Claim 1 or Claim 2 wherein said taurolidine and/or taurultam is administered at a dosage in the range of 150-450 mg/kg per day.
- 4. A method as claimed in Claim 3 wherein said taurolidine and/or taurultam is administered at a dosage in the range of 300 to 450 mg/kg per day.
- 5. A method as claimed in any one of Claims 1 to 4 for the treatment or prophylaxis of lymphomas, sarcomas, melanomas and carcinomas.
- 6. A method as claimed in any one of Claims 1 to 5 further comprising administering to said mammalian subject separately or simultaneously cytotoxic agents or agents known to be involved in tumour metabolism.
- 7. A method as claimed in Claim 6 comprising further administering gamma-interferon, interleukin-1, interleukin-2, adriamycin or actinomycin D.

- 8. Use of taurolidine and/or taurultam for the treatment or prophylaxis of tumours in mammalian subjects.
- 9. Use of taurolidine and/or taurultam for the preparation of pharmaceutical compositions for the treatment or prophylaxis of tumours in mammalian subjects.
- 10. A pharmaceutical composition comprising taurolidine and/or taurultum and at least one agent selected from cytotoxic agents or agents involved in tumour metabolism for separate or simultaneous administration to a mammalian subject suffering from or at risk to tumour growth.

International Application No

PCT/EP 91/01269 ·

I. CLASSI	IFICATION OF SUBJ	ECT MATTER (if several classification	on symbols apply, indicate all) ⁶	<u> </u>
	g to International Patent	t Classification (IPC) or to both Nations A 61 K 31/54		
II. FIELDS	S SEARCHED			
		Minimum Doc	cumentation Searched ⁷	
Classificat	ition System		Classification Symbols	
Int.C1	1.5	A 61 K		
			ther than Minimum Documentation nts are Included in the Fields Searched ⁸	
7 2001	COASTIDERS			
		D TO BE RELEVANT®	12	
Category °	Citation of Do	ocument, 11 with Indication, where appro	opriate, of the relevant passages 14	Relevant to Claim No.13
P,X ·	England al.:"An Tissue	of the Royal College d, vol. 72, 1990, M.E ntiseptic Toxicity to Culture: An Adjuvant y?", pages 388-392, s	E. Lucarotti et Breast Carcinoma in	9
A		139534 (Ed. GEISTLIC B5, see abstract; cla		9,10
A	Pharmac Pharmac	Reynolds: "Martindal copoeia, 29th Edition ceutical Press, (Lond lidine", see the whol	, 1989, The lon, GB), page 162,	9,10
"A" docuces "E" earli filing "L" documentation which citati "O" documentation when "P" documentation	isidered to be of particulier document but publis ng date ument which may throw ch is cited to establish to tion or other special rea cament referring to an or er means ament published prior to be than the priority date	eral state of the art which is not lar relevance shed on or after the interactional doubts on priority claim(s) or the publication date of another ison (as specified) and disclosure, use, exhibition or to the international filing date but	"T" later document published after the intern or priority date and not in conflict with a cited to understand the principle or theor invention "X" document of particular relevance; the cise cannot be considered novel or cannot be involve an inventive step "Y" document of particular relevance; the cise cannot be considered to involve an inventive step example to considered to involve an inventive document is combined with one or more ments, such combination being obvious the in the art. "A" document member of the same patent fail	the application but ry underlying the timed invention considered to timed invention tive step when the other such docu- to a person skilled
	Actual Completion of th	in International Search	Date of Mailing of this International Sea	nah Danad
	30-09-19		1 4. 10. 91	rca Report
International	Searching Authority EUROPEA	N PATENT OFFICE	Signature of Authorized Officer M. PEIS	Pes

International Application No. PC1/ EF91 /01209

Annals of Royal College of Surgeons of England, vol. 66, No. 3, May 1984, Henry C. Umpleby et al.: "The Efficacy of Agents Employed to Prevent Anastomotic Recurrence in Colorectal Carcinoma", pages 192–194, see the whole document Colorectal Carcinoma", Pot Colorectal Carcinoma", Pot Colorectal Carcinoma", Pot Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Carcinoma Colorectal Car	THES!	NFORMATION CONTINUED FROM THE SECOND SHEET	
Annals of Royal College of Surgeons or England, vol. 66, No. 3, May 1984, Henry C. Umpleby et al.: "The Efficacy of Agents Employed to Prevent Anastomotic Recurrence in Colorectal Carcinoma", pages 192–194, see the whole document Work	Ciber (
vol. 66, No. 3, May 1994, Merry C. Joseph Control of the control o	Ì	a n 1 Callage of Summons of Fnoland	9
al: "The Efficacy of Agents Employed to Prevent Anastomotic Recurrence in Colorectal Carcinoma", pages 192–194, see the whole document	X I	Annals of Royal College of Surgeons of England,	
Anastomotic Recurrence in Colorectal Carcinomal*, pages 192–194, see the whole document	.	MAULIUXA MUNTY I. URDIEDY EV	1
Anastomotic Recurrence in whole document			
pages 192-194, see the Whole document		Anactomotic Recurrence In Culticutal Cultiforms ;	·
IN OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE! Is international search report has not been established in respect of certain claims under Article (17(2))e) for the following reasons: In claim numbers 1-8 because they relate to subject matter not required to be searched by this Authority, namely. PIS. see Rule 39:1(1v) - PCT Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. Claim numbers with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. Claim numbers with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. Claim numbers the second and third sentences of PCT Rule 6.4(a). Decause they are dependent claims and are not drafted in accordance with second and third sentences of PCT Rule 6.4(a). This international Searching Authority found multiple inventions in this International application as Inflower: 1. As all required additional search fees were density paid by the applicant, this international search report covers only those claims of the international application for which fees ware paid, specifically claims. 2. As only some of the required additional search fees were timely paid by the applicant. Consequently, this international search report covers only the invention first mentioned in the claims, it is covered by claim numbers: 1. Por required additional search here without effort justifying an additional fee, the International Searching Authority did not pixely payers to day additional fee.		Anastomotic Recurrent whole document	
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers	!	pages 192-194, see the whole accommo	
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			1
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers]
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			į (
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			[
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			
his international search report has not been established in respect of certain classes they relate to subject matter not required to be searched by this Authority, namely. Claim numbers			
his international search report has not been established in respect of certain classes such as they relate to subject matter not required to be searched by this Authority, namely. Claim numbers		TOURS LINES APCHABLE 1	
his international search report has not been established in respect of certain classes such as they relate to subject matter not required to be searched by this Authority, namely Pls. see Rule 39:1(4v) - PCT Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. Claim numbers with the prescribed requirements to such an extent that no meaningful international sparch can be carried out, specifically. Claim numbers with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. Claim numbers the second and third sentences of PCT Rule 6.4(a). DESERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this international application as follows: 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application for which fees were paid, specifically claims. 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims. 4. Por required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers. The additional search fees were accompanied by applicant's protest.	TXI OF	SERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCH DATE (17/2) (or the fell	owing reasons:
No. Search numbers 1 -8	hie Interna	A STATE OF THE PROPERTY OF CHILDING CHILDS OF THE PROPERTY OF	uired to be searched by this
Authority, namely. Pls. see Rule 39.1(iv) - PCT Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic mehtods. Claim numbers with the prescribed requirements to such an extant that no meaningful international search can be carried out, specifically. Localized they are dependent claims and are not directed in accordance with the second and third sentances of PCT Rule 6.4(a). Mill OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this international application as follows: 1. As all vegured additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application for which fees were paid, specifically claims: 2. No required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international specification for which fees were paid, specifically claims: 1. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first restricted in the claims; it is covered by claim numbers: 1. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not limits payment of any additional fee. Remark on Protest		Person many	
Pls. see Rule 39.1(17) Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. Claim numbers	And	m numeric	
Method for treatment of as diagnostic mehtods. Claim numbers Decause they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. Claim numbers Decause they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. Claim numbers Decause they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8.4(a).	P 1	s. see Rule 39.1(1V) - rul	
ctaim numbers with the prescribed requirements to such an existing that no manningful international search can be carried out, specifically. Claim numbers with the prescribed requirements to such an existing that no manningful international search can be carried out, specifically. Claim numbers the second and third sentences of PCT Rule 6.4(a). Decause they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a). Deservations Where Unity of Invention is this international application as follows: 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application for which fees were paid, specifically claims: 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 3. We required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers. 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not timite payment of any additional fee. The additional search fees were accompanied by applicant's protest.	Me	thod for treatment of the numan or animal body	
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. Claim numbers the second and third sentences of PCT Rule 6.4(a). DESERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this international application as follows: As all required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers. Heremark on Protest The additional search fees were accompanied by applicant's protest.	1.10	therapy as well as diagnostic mentous.	·
Claim numbers with the prescribed requirements to such an extent that no meaningful international search can be cause they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a). Claim numbers the second and third sentences of PCT Rule 6.4(a). OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this international application as follows: As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application for which fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the unvention first mentioned in the claims; it is covered by claim numbers: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the unvention first mentioned in the claims; it is covered by claim numbers:	or	therapy, as were	
Claim numbers with the prescribed requirements to such an extent that no meaningful international search can be cause they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a). Claim numbers the second and third sentences of PCT Rule 6.4(a). OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this international application as follows: As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application for which fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the unvention first mentioned in the claims; it is covered by claim numbers: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the unvention first mentioned in the claims; it is covered by claim numbers:			
Claim numbers with the prescribed requirements to such an extent that no meaningful international season.		the parts of the internative	onal application that do not comply
Decause they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a). VI OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this International application as follows: 1. As all required additional search fees were their paid by the applicant, this international search report covers all searchable claims of the international application. 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims. 3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention that mentioned in the claims; it is covered by claim numbers. 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not make payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.		because they relate to perfect our be carned our	t, specifically:
Decause they are dependent claims and are not drafted in accordance with the second and third santences of PCT Rule 6.4(a). VI OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2 This international Searching Authority found multiple inventions in this International application as follows: 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention that mentioned in the claims; it is covered by claim numbers: 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not make payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	Mi. Cla	in humbers have requirements to such an extent that no meaningle.	
Claim numbers the second and third sentences of PCT Rule 6.4(a).	•		
Claim numbers the second and third sentences of PCT Rule 6.4(a).			•
Claim numbers the second and third sentences of PCT Rule 6.4(a).			•
Claim numbers the second and third sentences of PCT Rule 6.4(a).			
Claim numbers the second and third sentences of PCT Rule 6.4(a).			
Claim numbers the second and third sentences of PCT Rule 6.4(a).			
Claim numbers the second and third sentences of PCT Rule 6.4(a).		they are dependent claims and ar	e not drafted in accordance with
OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2	\Box		
This international Searching Authority found multiple inventions in this international search report covers all searchable claims of the international application 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 2. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentionad in the claims; it is covered by claim numbers: 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. 7. Remark on Protest 1. The additional search fees were accompanied by applicant's protest.	3 — 0	e second and third sentences of PCT Rule 6.4(a).	
This international Searching Authority found multiple inventions in this international search report covers all searchable claims of the international application 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 2. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentionad in the claims; it is covered by claim numbers: 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. 7. Remark on Protest 1. The additional search fees were accompanied by applicant's protest.			
1. As all required additional search feas were timely paid by the applicant, this international search report covers all searchable claims of the international application. 2. As only some of the required additional search feas were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentionad in the claims; it is covered by claim numbers: 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. The additional search fees were accompanied by applicant's protest.	VI.	OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING	
1. As all required additional search (see were timely paid by the applicant, this international search report covers all searchable claims of the international application. 2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. 7. Remark on Protest The additional search fees were accompanied by applicant's protest.			•
As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentional in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	11112 1111-		
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	•		
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.			
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentional in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.			
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentional in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.		and the state of t	wers all searchable claims
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.		to a week firmety paid by the applicant, this international search report	
2 As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: 4. As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.		at a suited additional sealon less were union, your	
No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	1. 🗆	is all required additional search reas were unitry	
No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	İ	of the international state and this international st	earch report covers only
No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	İ	of the international state and this international st	earch report covers only
As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	İ	of the international state and this international st	earch report covers only
As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	of the international applicant, this international search fees were timely paid by the applicant, this international st As only some of the required additional search fees were timely paid, specifically claims: those claims of the international application for which fees were paid, specifically claims:	earch report covers only
As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international so those claims of the international application for which fees were paid, specifically claims:	earch report covers only
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee. Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international so those claims of the international application for which fees were paid, specifically claims:	earch report covers only
Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international so those claims of the international application for which fees were paid, specifically claims:	earch report covers only
Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international states of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search fees were timely paid by the applicant. Consequently, this international search fees were timely paid by the applicant.	earch report covers only rch report is restricted to
Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international states of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search fees were timely paid by the applicant. Consequently, this international search fees were timely paid by the applicant.	earch report covers only rch report is restricted to
Remark on Protest The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international states of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search fees were timely paid by the applicant. Consequently, this international search fees were timely paid by the applicant.	earch report covers only rch report is restricted to
The additional search fees were accompanied by applicant's protest.	2 🗆	As only some of the required additional search fees were timely paid by the applicant, this international so those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search invantion first mentioned in the claims; it is covered by claim numbers:	earch report covers only rch report is restricted to
The additional search fees were accompanied by applicant's protest. No protest accompanied the payment of additional search fees.	2 .	As only some of the required additional search fees were timely paid by the applicant, this international so those claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international seather invantion first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Solimite payment of any additional fee.	earch report covers only rch report is restricted to
No protest accompanied the payment of additional search (sea.	2 .	As only some of the required additional search fees were timely paid by the applicant, this international states of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Scients payment of any additional fee.	earch report covers only rch report is restricted to
No protest accompanied the payment or adminutes seem to	2 .	As only some of the required additional search fees were timely paid by the applicant, this international states of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search invention first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Scients payment of any additional fee.	earch report covers only rch report is restricted to
	2 .	As only some of the required additional search fees were timely paid by the applicant, this international subthose claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search invantion first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Solution Protest The additional search fees were accompanied by applicant's protest.	earch report covers only rch report is restricted to
	2 .	As only some of the required additional search fees were timely paid by the applicant, this international subthose claims of the international application for which fees were paid, specifically claims: No required additional search fees were timely paid by the applicant. Consequently, this international search invantion first mentioned in the claims; it is covered by claim numbers: As all searchable claims could be searched without effort justifying an additional fee, the international Solution Protest The additional search fees were accompanied by applicant's protest.	earch report covers only rch report is restricted to

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

. EP 9101269 SA 48878

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/10/91

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document	Publication	Patent family		Publication date
cited in search report	date	member(s)		
EP-A- 0139534	02-05-85	AU-A- BE-A- CH-A- DE-A- JP-A- US-A-	3457484 900855 660969 3438470 60105617 4604391	09-05-85 15-02-85 30-06-87 30-05-85 11-06-85 05-08-86